PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MARY E. BAK
HOWSON AND HOWSON
SPRING HOUSE CORPORATE CENTER
P.O. BOX 457
SPRING HOUSE, PA 19477

PCT

REC'D 25 NOV 2005
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	23 NOV 2005
Applicant's or agent's file reference TUL6PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/02023	21 January 2005 (21.01.2005)	23 January 2004 (23.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 38/00, C12N 15/00, 15/06, 15/07; G01N 33/20 and US Cl.: 530/350, 387; 514/2; 435/440, 7.1, 7.8; 424/278.1

Applicant

THE ADMINISTRATOR OF THE TULANE EDUCATIONAL FUND

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☒ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Samuel W. Liu Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☒ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-19	YES
	Claims 20	NO
Inventive step (IS)	Claims 1-19	YES
	Claims 20	NO
Industrial applicability (IA)	Claims 1-20	YES
	Claims NONE	NO

2. Citations and explanations:

Claim 20 lacks novelty under PCT Article 33(2) and inventive step under PCT Article 33(3) as being anticipated by and obvious over, respectively, by Bejanin et al. (WO 02/083898).

In the patent claims 14 and page 163, Bejanin et al. teach a polypeptide of SEQ ID NO: 254 consisting of amino acids residues 1-62 which is a structurally derivative (variant) to the instant SEQ ID NO:4 polypeptide (residues 1-61) which is a variant metallothionein (MT) and defective in binding to megalin receptor. The Bejanin et al. variant polypeptide has at least 88% sequence identity to said SEQ ID NO:4 polypeptide, and does not bind megalin as avidly as naturally-occurring MT protein because of the reasons set forth below.

The consensus sequence (core sequence) "SCKKSC" (residue 29-35) of wild-type MT (the instant SEQ ID NO:1), i.e., "SCXXSC" (wherein "X" is not lysine) in the SEQ ID NO:4 sequence, is critical for binding of the variant MT to the megalin receptor. Structural alteration in this consensus sequence leads to great reduction of the variant MT binding to megalin (see Table 4 and pages 46-47 of the specification). The Bejanin et al. variant MT polypeptide only has alteration in this consensus sequence (see residue 31) but also deletion mutation in the adjacent region to the consensus sequence (see residue 8). Thus, The Bejanin's variant polypeptide does not bind megalin as avidly as naturally occurring MT, which is applied to instant claim 20.

Claims 1-19 meet the criteria set out in PCT Article 33(2) and (3) because the prior art does not teach or fairly suggest the claimed composition and the method of using the said composition for treating cancer and/or inhibiting renal uptake of therapeutic divalent metal ions.

Claims 1-20 meet the requirement of PTC article 33(4), because the claimed compositions are useful in treating heavy metal-mediated poisoning effect in kidney and inhibiting renal uptake of therapeutic metal ions.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 18 recitation "use of the composition of claim 1..." is objected to as containing the following defect(s) under PCT Rule 66.2(a)(iii) in the form or contents thereof:
Claim 18 does not set forth any step(s) involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claim 20 lacks novelty under PCT Article 33(2) and inventive step under PCT Article 33(3) as being anticipated by and obvious over, respectively, by Bejanin et al. (WO 02/083898).

In the patent claims 14 and page 163, Bejanin et al. teach a polypeptide of SEQ ID NO: 254 consisting of amino acids residues 1-62 which is a structurally derivative (variant) to the instant SEQ ID NO:4 polypeptide (residues 1-61) which is a variant metallothionein (MT) and defective in binding to megalin receptor. The Bejanin et al. variant polypeptide has at least 88% sequence identity to said SEQ ID NO:4 polypeptide, and does not bind megalin as avidly as naturally-occurring MT protein because of the reasons set forth below.

The consensus sequence (core sequence) "SCKKSC" (residue 29-35) of wilt-type MT (the instant SEQ ID NO:1), i.e., "SCXXSC" (wherein "X" is not lysine) in the SEQ ID NO:4 sequence, is critical for binding of the variant MT to the megalin receptor. Structural alteration in this consensus sequence leads to great reduction of the variant MT binding to megalin (see Table 4 and pages 46-47 of the specification). The Bejanin et al. variant MT polypeptide only has alteration in this consensus sequence (see residue 31) but also deletion mutation in the adjacent region to the consensus sequence (see residue 8). Thus, The Bejanin's variant polypeptide does not bind megalin as avidly as naturally occurring MT, which is applied to instant claim 20.

Claims 1-19 meet the criteria set out in PCT Article 33(2) and (3) because the prior art does not teach or fairly suggest the claimed composition and the method of using the said composition for treating cancer and/or inhibiting renal uptake of therapeutic divalent metal ions.

Claims 1-20 meet the requirement of PTC article 33(4), because the claimed compositions are useful in treating heavy metal-mediated poisoning effect in kidney and inhibiting renal uptake of therapeutic metal ions.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MARY E. BAK
HOWSON AND HOWSON
SPRING HOUSE CORPORATE CENTER
P.O. BOX 457
SPRING HOUSE, PA 19477

PCT

REC'D 25 NOV 2005
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	23 NOV 2005
Applicant's or agent's file reference TUL6PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US05/02023	21 January 2005 (21.01.2005)	23 January 2004 (23.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 38/00, C12N 15/00, 15/06, 15/07; G01N 33/20 and US Cl.: 530/350, 387; 514/2; 435/440, 7.1, 7.8; 424/278.1

Applicant

THE ADMINISTRATOR OF THE TULANE EDUCATIONAL FUND

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☒ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Samuel W. Liu
Telephone No. 571-272-1600

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☒ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-19	YES
	Claims 20	NO
Inventive step (IS)	Claims 1-19	YES
	Claims 20	NO
Industrial applicability (IA)	Claims 1-20	YES
	Claims NONE	NO

2. Citations and explanations:

Claim 20 lacks novelty under PCT Article 33(2) and inventive step under PCT Article 33(3) as being anticipated by and obvious over, respectively, by Bejanin et al. (WO 02/083898).

In the patent claims 14 and page 163, Bejanin et al. teach a polypeptide of SEQ ID NO: 254 consisting of amino acids residues 1-62 which is a structurally derivative (variant) to the instant SEQ ID NO:4 polypeptide (residues 1-61) which is a variant metallothionein (MT) and defective in binding to megalin receptor. The Bejanin et al. variant polypeptide has at least 88% sequence identity to said SEQ ID NO:4 polypeptide, and does not bind megalin as avidly as naturally-occurring MT protein because of the reasons set forth below.

The consensus sequence (core sequence) "SCKKSC" (residue 29-35) of wild-type MT (the instant SEQ ID NO:1), i.e., "SCXXSC" (wherein "X" is not lysine) in the SEQ ID NO:4 sequence, is critical for binding of the variant MT to the megalin receptor. Structural alteration in this consensus sequence leads to great reduction of the variant MT binding to megalin (see Table 4 and pages 46-47 of the specification). The Bejanin et al. variant MT polypeptide only has alteration in this consensus sequence (see residue 31) but also deletion mutation in the adjacent region to the consensus sequence (see residue 8). Thus, The Bejanin's variant polypeptide does not bind megalin as avidly as naturally occurring MT, which is applied to instant claim 20.

Claims 1-19 meet the criteria set out in PCT Article 33(2) and (3) because the prior art does not teach or fairly suggest the claimed composition and the method of using the said composition for treating cancer and/or inhibiting renal uptake of therapeutic divalent metal ions.

Claims 1-20 meet the requirement of PTC article 33(4), because the claimed compositions are useful in treating heavy metal-mediated poisoning effect in kidney and inhibiting renal uptake of therapeutic metal ions.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 18 recitation "use of the composition of claim 1..." is objected to as containing the following defect(s) under PCT Rule 66.2(a)(iii) in the form or contents thereof:
Claim 18 does not set forth any step(s) involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/02023

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claim 20 lacks novelty under PCT Article 33(2) and inventive step under PCT Article 33(3) as being anticipated by and obvious over, respectively, by Bejanin et al. (WO 02/083898).

In the patent claims 14 and page 163, Bejanin et al. teach a polypeptide of SEQ ID NO: 254 consisting of amino acids residues 1-62 which is a structurally derivative (variant) to the instant SEQ ID NO:4 polypeptide (residues 1-61) which is a variant metallothionein (MT) and defective in binding to megalin receptor. The Bejanin et al. variant polypeptide has at least 88% sequence identity to said SEQ ID NO:4 polypeptide, and does not bind megalin as avidly as naturally-occurring MT protein because of the reasons set forth below.

The consensus sequence (core sequence) "SCKKSC" (residue 29-35) of wilt-type MT (the instant SEQ ID NO:1), i.e., "SCXXSC" (wherein "X" is not lysine) in the SEQ ID NO:4 sequence, is critical for binding of the variant MT to the megalin receptor. Structural alteration in this consensus sequence leads to great reduction of the variant MT binding to megalin (see Table 4 and pages 46-47 of the specification). The Bejanin et al. variant MT polypeptide only has alteration in this consensus sequence (see residue 31) but also deletion mutation in the adjacent region to the consensus sequence (see residue 8). Thus, The Bejanin's variant polypeptide does not bind megalin as avidly as naturally occurring MT, which is applied to instant claim 20.

Claims 1-19 meet the criteria set out in PCT Article 33(2) and (3) because the prior art does not teach or fairly suggest the claimed composition and the method of using the said composition for treating cancer and/or inhibiting renal uptake of therapeutic divalent metal ions.

Claims 1-20 meet the requirement of PTC article 33(4), because the claimed compositions are useful in treating heavy metal-mediated poisoning effect in kidney and inhibiting renal uptake of therapeutic metal ions.